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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,027	WANG, JINHAI	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 6/4/04, claims 1-36 have been cancelled, and claims 37-70 added. (Applicants have asserted that claims 37-71 were added, but no claim 71 has been presented). Claims 37-70 are now pending.

Applicants' arguments filed 6/4/04 have been considered and found not persuasive.

✧

35 U.S.C. §101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claim 38 is rejected under 35 USC §101 because the claimed invention is not supported by a well established utility.

Claim 38 is drawn to a method of inhibiting apoptosis. While this may be beneficial under some circumstances, and for certain cell types, it will be deleterious under other circumstances, and for other cell types. Consider the following:

- Kanegane Hirokazu (*Pediatric nephrology* (Berlin, Germany) **18** (5) 454-6, 2003) discloses that mutations in the *Fas* gene result in impaired apoptosis (at least *Fas*-mediated apoptosis), and that as a result of this, autoimmune disease and glomerulonephritis occurs. Thus, one would conclude that inhibiting apoptosis will result in autoimmune disease and glomerulonephritis.

- Strasser A. (*Annals of the New York Academy of Sciences* **917**, 541-8, 2000) discloses that Bim is a member of the Bcl-2 family of proteins, and that Bim induces apoptosis. Strasser further discloses that Bim-deficient mice develop autoimmune disease and glomerulonephritis. Thus, one would conclude that inhibiting apoptosis will result in autoimmune disease and glomerulonephritis.

- Van Den Brande, Jan M. H. (*Annals of the New York Academy of Sciences* **973** 166-80, 2002) discloses that Crohn's disease can be treated by inducing T-lymphocyte apoptosis. The skilled artisan would conclude that if Crohn's disease can be treated by inducing apoptosis, then any attempt to inhibit apoptosis would only exacerbate the patient's condition.

- Kacinski B M (*Annals of the New York Academy of Sciences* **941**, 194-9, 2001 discloses that the methods of treating cutaneous T-cell lymphoma that are most successful act by inducing T-cell apoptosis. The skilled artisan would therefor conclude that if cutaneous T-cell lymphoma can be treated by inducing apoptosis, then any attempt to inhibit apoptosis would only exacerbate the patient's condition.

- Tsuchiyama Y (*Kidney International* **58** (5) 1941-52, 2000) discloses that galectin-9 is effective to treat nephritis, and that dexamethasone is also effective in this regard. Both of these agents induced apoptosis of splenic CD8+ cells. The skilled artisan would conclude that if nephritis can be treated by inducing apoptosis, then any attempt to inhibit apoptosis would only exacerbate the patient's condition.

- Li X. C. (*Current Opinion in Immunology* **12** (5) 522-7, 2000) discloses that T cell apoptosis is required for transplantation tolerance. The skilled immunologist would conclude that attempts to inhibit apoptosis would result in transplantation rejection.

- Bednarski Jeffrey J. (*Arthritis and rheumatism* **48** (3) 757-66, 2003) discloses that a compound designated Bz-423 induces apoptosis, and is effective to mitigate

> autoimmune disease such as glomerulonephritis and arthritis. The skilled immunologist would conclude that attempts to inhibit apoptosis would cause autoimmune disease, or at least exacerbate it.

In addition to the foregoing, there is the matter of inhibiting apoptosis in patients who are stricken with cancer, or persons who are pre-cancerous and predisposed to tumor growth. As applicants may recognize, inhibiting apoptosis is not going to be helpful. Thus, it is just as likely that inhibiting apoptosis will cause illness (or exacerbate it) as to mitigate it. Given that the effect of administering the claimed compounds is likely to be to cause illness, or to exacerbate an existing illness, it appears that the claimed compounds will not be useful.

Claim 38 is also rejected under 35 USC §112 first paragraph. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38, 40-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown that representative examples of the claimed compounds can inhibit caspases *in vitro*. It is likely to be true that for certain cell types, apoptosis will be inhibited. But the specification gives no guidance as to which cell types will exhibit reduced apoptosis, and which will not. As it happens, the skilled artisan who has observed inhibition of apoptosis in one cell line (as a consequence of incubation with compound "X") cannot "predict" what other cell lines will undergo reduced apoptosis in the presence of compound "X". The skilled artisan also cannot predict what other cell types will undergo enhanced apoptosis in the presence of compound "X". For example, Fang X. (*Biochemical Journal* **352 Pt 1** 135-43, 2000) discloses that lysophosphatidic acid inhibits apoptosis in fibroblasts; at the same time, Steiner M. R. (*Annals of the New York Academy of Sciences* **905** 132-41, 2000) discloses that lysophosphatidic acid induces apoptosis in neuronal cells. Thus, if a determination is made that a given compound will inhibit apoptosis of a given cell type, the skilled artisan cannot predict the cell types in which apoptosis will be inhibited, and the cell types in which apoptosis will be induced. This conclusion is reinforced by the findings of Tsuchiyama Y (*Kidney International* **58** (5) 1941-52, 2000) who discloses that while dexamethasone induces apoptosis in both CD8+ cells and CD4+ cells, Galectin-9 induces apoptosis in CD8+ cells, but fails to induce

apoptosis in CD4+ cells. Thus, a claim drawn to a method of inhibiting apoptosis of any and all cell types lacks enablement.

In addition to the foregoing, applicants are extrapolating from a showing of caspase inhibition *in vitro* to an assertion that all of the following diseases can be successfully treated: arthritis, metastasis, infectious diseases, meningitis, salpingitis, septic shock, respiratory diseases, inflammatory condition, cholangitis, colitis, encephalitis, endocerolitis, hepatitis, pancreatitis, reperfusion injury, ischemic diseases, myocardial infarction, stroke, ischemic kidney disease, immune-based diseases, hypersensitivity, auto-immune diseases, multiple sclerosis, bone diseases, neurodegenerative diseases, Alzheimer's Disease, Amylotrophic Lateral Sclerosis (ALS), Huntington's disease, Parkinson's disease, meningitis, spinal chord injuries, liver damage, traumatic brain injury, alopecia, AIDS and toxin-induced liver disease.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Consider, for example, the following:

- Frost, Robert A. (*American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **283** (3) R698-709, 2002) investigated the regulation of TNFα and IL-6 by lipopolysaccharide (LPS) in C2C12 myoblasts and mouse skeletal muscle. Treatment of myocytes with IL-1 or TNF-alpha also increased IL-6 mRNA content, and the increase in IL-6 mRNA due to LPS could not be prevented by pretreatment with antagonists to either IL -1 or TNF. Thus, even if applicants could successfully block all interleukin-1 production using the claimed compounds, interleukin-6 levels could not be controlled, thereby leading to "unpredictable" results on inflammatory response.

- Meyers, K. P. (*Inflammation* **17** (2) 121-34, 1993) discloses that interleukin-1 receptor antagonist was not active as an antiinflammatory agent in the 24-h pleurisy model (carageenan-induced pleurisy).

- Rosenbaum J. T. (*Archives of Ophthalmology* **110** (4) 547-9, 1992) discloses that interleukin-1 receptor antagonist did not produce significant reduction in inflammation subsequent to an active Arthus reaction or subsequent to the intravitreal injection of 125 ng of endotoxin. Rosenbaum suggests that the failure of IL-1RA to be therapeutically effective may be due in part to the presence of other pro-inflammatory cytokines.

- Brennan (*Clinical and Experimental Immunology* **81**, 278-85, 1990) discloses that TGF-β was effective to inhibit IL-1β production in LPs-stimulated peripheral blood mononuclear cells, but only if the cells were pretreated with TGF-β. The IL-1β production was not inhibited if the TGF-β was applied after the inducing stimulus. The point here is that if a scientist has evidence that a given agent "X" is effective to inhibit production of IL-1β when used prior to stimulation of cells (which stimulation produces the IL-1β), attempting to inhibit production of IL-1β by using agent "X" after stimulation of the cells leads to "unpredictable" results.

- Paris (*Journal of Infectious Diseases* **171**, 161-69, 1995) discloses that IL-1RA was not effective to treat inflammation caused by gram-negative bacteria.

If it were really true that inhibiting the production of interleukin-1 were effective to treat inflammatory conditions, then the skilled artisan would have expected therapeutic success to

follow inevitably from such inhibition, or from inhibiting the activation of the receptor for IL-1. However, this is not what one finds. Accordingly, the skilled artisan would expect that in endeavoring to treat inflammatory disorders using compounds that mitigate the production of or efficacy of IL-1, "unpredictable" results will be obtained. Consider also the following:

- Saez-Torres (*Clinical and Experimental Immunology* **121**, 151, 2000 discloses that peptide T inhibits T cell activation and cytokine production, but that it was not effective *in vivo* to treat EAE (experimental automimmune encephalomyelitis). This supports the assertion that where inflammation and neurodegenerative disorders are concerned, one cannot "predict" therapeutic efficacy on the basis of an *in vitro* assay.

- Hill P. A., (*J Cell. Biochem* **56** (1) 118-30, 1994) discloses that a peptide inhibitor of cysteine proteases is not an effective inhibitor of bone resorption. Thus, one cannot predict the propensity of a compound to inhibit bone resorption based on its propensity to inhibit a thiol protease.

- Steinberg (*The Scientist* **16**, 22, 2002) discloses that when researchers vaccinated transgenic mice that had developed AD-like pathology, placques "melted away". In addition, favorable results were obtained in cognitive experiments with the mice. However, when attempted in humans, the Alzheimer's symptoms worsened. The point here is that where Alzheimer's disease is concerned, extrapolation from experimental result in animals to humans leads to unpredictable results. Steinberg went much further than applicants have, in that he carried out experiments in animals. If extrapolating from rats to humans leads to unpredictable results, it stands to reason that extrapolating from the test tube to diseased humans will also lead to unpredictable results.

- Kitazawa R (*Journal of Clinical Investigation* **94** (6) 2397-406, 1994) investigated factors affecting osteoclastogenesis. Kitazawa discloses that anti-IL-6 Ab inhibited bone resorption *in vitro* but not *in vivo*. Thus, where bone disease is concerned, the skilled artisan would conclude that in attempting to extrapolate form the petri dish to the human, "unpredictable" results are obtained.

- Read S. J. (*Drugs and Aging* **14** (1) 11-39, 1999) discloses (e.g., abstract) that although many drugs are effective in animal models of cerebral ischemia, these drugs have largely failed to fulfil their promise in clinical trials. Applicants have argued that if a compound can inhibit a caspase in vitro, it will be effective to treat ischemia in a human. However, given that extrapolation from animals to humans leads to unpredictable results, it stands to reason that extrapolating from the test tube to diseased humans will also lead to unpredictable results.

Applicants are also asserting that they can successfully treat any and all "infectious diseases". The nature of such diseases is not specified but would include diseases resulting from a bacterial infection, such as one of the following: Anthrax, Bovine Spongiform, Encephalopathy (BSE), Chicken Pox, Cholera, Conjunctivitis, Creutzfeldt-Jakob Disease, Polio, Nosocomial Infections, Otitis Media, Pelvic Inflammatory disease, Plague, Pneumonia, Dengue Fever, Elephantiasis, Encephalitis, Fifth's Disease, Rabies, Rheumatic Fever, Roseola, Rubella, Sexually Transmitted diseases, Helicobacter Pylori, Smallpox, Strep Throat, septicemia, sickle cell anemia, ulcers, Tetanus, Toxic Shock Syndrome, Lassa Fever, Leprosy, Lyme Disease, Typhoid Fever, Measles, Meningitis, Trachoma, Toxoplasmosis, Tuberculosis, Whooping Cough, and Yellow Fever. In addition to the foregoing, viral infections (e.g., hepatitis, HIV, picornavirus) and fungal infections (e.g., candida albicans) would be included. Diseases resulting from parasitic infections would also be included, such as malaria, trypanosomiasis, schistosomiasis, onchocerciasis, leishmaniasis, amebiasis, ascariasis, babesiosis, balantidiasis, enterobius, fiarisis, blood

flukes, giaridasis, hookworm, strongyloidiasis, tapeworm, toxoplasmosis, trichinosis, and trichuriasis. As it happens, there is "unpredictability" here too. The following references pertain to fungal infections:

- Buchta, V. (*Mycoses* **44** (11-12) 505-12, 2001) discloses that a patient died from a fungal infection despite being treated with compounds that exhibit anti-fungal activity *in vitro*.

- Adam (*Medicine* **65**, 203, 1986) discloses (page 208, col 2) that *in vitro* susceptibility to antifungal agents did not correlate with therapeutic efficacy of the agents.

- Nagasawa M. (*Journal of Infection* **44** (3) 198-201, 2002) discloses that a patient died from a fungal infection despite being treated with compounds that exhibit anti-fungal activity *in vitro*.

- Manfredi R (*Mycopathologia* **148** (2) 73-8, 1999) discloses that two patients died from a cyrotpococcus infection despite being treated with an agent that exhibited anti-fungal activity *in vitro*.

- Wang M. X. (*Cornea* **19** (4) 558-60, 2000) discloses that a patient was treated with an agent that exhibited anti-fungal activity *in vitro*, but that despite this, his fungal sclerokeratitis progressed to endophthalmitis.

- Bhalodia M V (*Journal of the Association for Academic Minority Physicians* **9** (4) 69-71, 1998) discloses that a compound that exhibited anti-fungal activity *in vitro* was not effective to treat a candida infection in a patient.

- Moore M. L. (*Journal of Perinatology* **21** (6) 399-401, 2001) discloses that a premature infant died from a fungal infection despite being treated with a compound that exhibits anti-fungal activity *in vitro*.

- Berman, Judith (*Nat Rev Genet* **3** (12) 918-30, 2002) discloses that many immunocompromised patients die from *Candida* infections in spite of having received various dosages of compounds which exhibit anti-fungal activity *in vitro*.

- van Duin David (*Antimicrobial Agents and Chemotherapy* **46** (11) 3394-400, 2002)

has disclosed an example of a compound which exhibits antifungal activity *in vitro* but not *in vivo*.

- Marr K. A. (*Antimicrobial Agents and Chemotherapy* 45 (1) 52-9, 2001) discloses that a patient developed a fungal infection despite prophylactic treatment with a compound which exhibits antifungal activity *in vitro*.

Thus, even if applicants had demonstrated that the claimed compounds can inhibit growth of fungi *in vitro*, it would still follow therefrom that successful treatment of "infections" in animals could not be predicted. "Infections", of course, would include those caused by bacteria. For example, the following would be encompassed:

> Anthrax, cholera, conjunctivitis, nosocomial infections, otitis media, pelvic inflammatory disease, plague, pneumonia, dengue fever, elephantiasis, rabies, rheumatic fever, roseola, rubella, syphillis, gonnorhea, clamydia, helicobacter pylori, "mucosa-associated lymphoid tissue" resulting from helicobacter pylori, smallpox, strep throat, septicemia, sickle cell anemia, ulcers, tetanus, toxic shock syndrome, lassa fever, leprosy, lyme disease, typhoid fever, measles, meningitis, trachoma, toxoplasmosis, tuberculosis, whooping cough, yellow fever, vancomycin-resistant staphylococcus, diarrhea, brucellosis, diptheria, coccidiodiomycosis, and cold sores.

Several of the claims (e.g., 64-70) encompass treatment of HIV/AIDS. With respect thereto, consider the following:

- Mangos (*Texas Medicine*, **86**, 40, 1990) states the following:

  "In spite of ... [therapy against HIV and opportunistic infections], the universal outcome of HIV infection / AIDS is the death of the patients" (see, e.g., abstract).

- As disclosed in Binquet (*AIDS* **12**, 2313, 1998) a total of 556 patients were treated with HIV protease inhibitors for a period of 230 days, and that despite being treated with with HIV protease inhibitors for more than seven months, 24 of the patients had

died. Both this reference, and Mangos, teach that death occurs in spite of administration of HIV protease inhibitors. If death is the result of a treatment, one cannot say that success (in the treatment) is predictable.

- Erickson (*Ann Rev Pharm Toxicol* **36**, 545-71, 1996) discloses that resistance of HIV to drugs is a significant problem, and discusses some of the biochemical mechanisms by which such resistance is conferred.

- Matsushita (*Int J Hematol* **72**, 20-27, 2000) discloses that the benefits of anti-HIV therapy, to the extent that they occur at all, are merely transient when only just one or two agents are used.

These references (Mangos, Binquet, Erickson or Matsushita) support the proposition that even if one can demonstrate inhibition of HIV replication *in vitro*, one cannot "predict" therapeutic efficacy in an attempted treatment of an AIDS patient.

It is not apparent that any of the recited diseases can be successfully treated by the claimed compounds. The reality is that attempting to extrapolate from *in vitro* data to a therapy in humans (or other mammals) leads to "unpredictable" results. For example, Otvos "Insect peptides with improved protease-resistance protect mice against bacterial infection" (*Protein Science* **9** (4) 742-9, 2000) discloses one peptide that is active *in vitro* but not *in vivo* (due to the rapid decomposition in mammalian sera). In the field of ulcer treatment, one may look to the following references, which disclose "failure" in the treatment of such, in spite of *in vitro* efficacy in inhibition of *Helicobacter*:

Phillips, (*Helicobacter* 6, 151, 2001);

Pilotto (*Digestive and Liver Disease* 32 (8) 667-72, 2000);

Leung (*Expert Opin Pharmacother* 1 (3) 507-14, 2000).

As for the issue of antibiotic resistance, the following references discuss this:

Liu (*Advances in Experimental Medicine and Biology* 455, 387 1999)

Monroe (*Current Opinion in Microbiology* 3(5) 496-501, 2000).

Specifically with regard to endotoxin-associated conditions, consider the following: Corriveau C. C. "Antiendotoxin therapies for septic shock" (*Infectious Agents and Disease*, **2** (1) 44-52, 1993) discloses that there have been numerous attempts over the years to treat human septic shock by inhibiting, neutralizing, or clearing endotoxin, and that the results of those attempts support a conclusion of "unpredictability" in the treatment of the same. Thus, extrapolation from *in vitro* data to a therapy in humans (or other mammals) leads to "unpredictable" results.

In response to the foregoing, applicants have argued that (a) they have added a claim drawn to a method of inhibiting a caspase, and a claim to a method of inhibiting apoptosis, (b) the examiner has stipulated that both claims in (a) are enabled, and (c) since the claims in (a) are enabled, it follows therefrom that any claim which is recited to be dependent thereon must be enabled. However, applicants conclusions are not correct, and moreover, the previous characterization of what is now claim 38 as enabled is revoked herewith (note that there has been a change of supervisors). In addition, applicants have not even

acknowledged the examiner's rejection of claims that are drawn to "pharmaceutical" compositions. A first step in overcoming a rejection is to acknowledge it, and the second step is to traverse it. Applicants have done neither, at least where "pharmaceutical" composition claims are concerned. Nor is applicants' premise correct, i.e., that if a claim is enabled, any claim which is recited to be dependent thereon must be enabled as well. What matters is what is recited in a given claim; in the case of a dependent claim, what matters also is that which is "carried over" from the claim on which it depends. The fact that a given claim may be enabled does not "immunize" all claims dependent thereon from enablement rejection. If a claim is drawn to a compound, and that claim is enabled, this does not mean that a claim drawn to a method of treating a disease will be enabled merely because it is dependent on the claim drawn to the compound. Even if claim 38 were now to be characterized as enabled, it would not follow therefrom that e.g., claim 64 is enabled. Claim 64 is dependent ultimately on claim 38. Claim 64 recites "the method of treatment of claim 40". This phrase lacks antecedent basis, although that is not the point. The point is that claim 64 asserts, or at least implies, therapeutic efficacy, which claim 38 does not. Thus, even if claim 38 were now to be characterized as enabled, it would not follow therefrom that claim 64 would be enabled. The real issue here is whether one can predict therapeutic efficacy (following adminstration to ill patients) on the basis of the observation that the claimed compounds can inhibit

caspases. It is suggested that applicants select (at least) one of the following diseases, and explain the basis upon which this assertion of predictability is made:

> arthritis, metastasis, infectious diseases, meningitis, salpingitis, septic shock, respiratory diseases, inflammatory condition, cholangitis, colitis, encephalitis, endocerolitis, hepatitis, pancreatitis, reperfusion injury, ischemic diseases, myocardial infarction, stroke, ischemic kidney disease, immune-based diseases, hypersensitivity, auto-immune diseases, multiple sclerosis, bone diseases, neurodegenerative diseases, Alzheimer's Disease, Amylotrophic Lateral Sclerosis (ALS), Huntington's disease, Parkinson's disease, meningitis, spinal chord injuries, liver damage, traumatic brain injury, alopecia, AIDS and toxin-induced liver disease.

Claims 64-70 recite immune-based disease, arthritis and hypersensitivity. Consider again the teachings of the following references:

Kanegane Hirokazu (*Pediatric nephrology* (Berlin, Germany) **18** (5) 454-6, 2003)

Strasser A. (*Annals of the New York Academy of Sciences* **917**, 541-8, 2000)

Van Den Brande, Jan M. H. (*Annals of the New York Academy of Sciences* **973** 166-80, 2002)

Kacinski B. M., *Annals of the New York Academy of Sciences* **941**, 194-9, 2001

Tsuchiyama Y (*Kidney International* **58** (5) 1941-52, 2000)

Li X. C. (*Current Opinion in Immunology* **12** (5) 522-7, 2000)

Bednarski Jeffrey J. (*Arthritis and rheumatism* **48** (3) 757-66, 2003)

These references support the proposition that autoimmune disease will be exacerbated when apoptosis is inhibited. This is opposite the effect that applicants are proposing. Accordingly, one cannot "predict" effective treatment of autoimmune disease by inhibiting

apoptosis. Claims 64-70 also recite that metastasis can be treated. This implies that applicants would want to inhibit apoptosis in a tumor-bearing patient. However, if a skilled medical practitioner were to inhibit apoptosis of tumor cells, he would end up shortening the patient's life. One cannot predict therapeutic success under such circumstances.

As a practical matter, applicants have not explained why the examiner's conclusion of "undue experimentation" might be incorrect. Accordingly, no further explanation by the examiner is required at this point.

It is suggested that the term "pharmaceutical" be deleted at every occurrence, that the term "therapeutically effective" be deleted at every occurrence, that the term "treatment" be deleted at every occurrence, and that any claim which recites or implies therapeutic efficacy be cancelled.

A matter unrelated to the foregoing concerns the term "protease inhibitor" in each of claims 40, 47, 59. Claim 47 (and 40 and 59) implies that the compounds can inhibit any protease. However, there is no evidence that this is the case. Applicants have shown only that the compounds can inhibit caspases. It is rarely the case that a compound can inhibit thiol proteases, metalloproteases, aspartyl proteases, endopeptidases and exopeptidases. There may be a few examples of such, but in most cases this is not what one finds. Issues concerning proteases, active sites of

proteases, and inhibition of proteases have been reviewed by Fersht (*Enzyme structure and Mechanism* pp. 18-28, and 302-324, WH Freeman & Co., 1977), Thompson (*Annual Reports in Medicinal Chemistry* **36**, 247-256, 2001) and Storer (*Perspect. Drug Discovery Des.* **6** (Cysteine Proteases), 33-46, 1996). As is evident, there are several classes of proteases, each of which has a different active site. While there may be a few isolated examples of compounds which can inhibit thiol proteases and serine proteases and aspartyl proteases, in general there is no "crossover" between inhibition of different proteases. As for the "working examples", applicants have only shown inhibition of caspases. As for the "unpredictability of the art", the following references are relevant:

- Johnson (USP 6,034,066) discloses (col 7, line 12) a protease that is inhibited by a cysteine protease inhibitor, but not by a serine protease inhibitor.
- Matsuo (USP 4,704,359) discloses (col 3, line 36+) a protease that is inhibited by a serine protease inhibitor, but not by a cysteine protease inhibitor.
- Sato (USP 4,479,937) discloses (col 2, line 30+) a compound which inhibits thiol proteases, but fails to inhibit serine proteases or acid proteases.

Thus, merely because a compound can inhibit a caspase that the compound will inhibit all cysteine proteases and all metalloproteases and all carboxypeptidases. The results of such an extrapolation are "unpredictable". In accordance with the foregoing, "undue experimentation" would be required to inhibit proteases other than caspases.

✧

Claims 37-70 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Each of claims 37-38 is dependent on a cancelled claim.

- Claim 39 makes reference to an "unnatural amino acid structure". What are the limits here? In particular, are *beta-* and *gamma-* amino acids included?

- Claim 40 recites "the method according to claim 38 for use as a protease inhibitor". However, this format is improper. First, the phrase "for use as a protease inhibitor" implies that a compound is being referred to, whereas claim 40 is drawn to a method. Second, the claim is drawn to a method of inhibiting apoptosis, not to a method of inhibiting a protease. Consider the following analogy:

  100. A method of transportation comprising acquiring an automobile and driving the automobile from one location to another.

  101. The method according to claim 100 for use as a device for converting chemical energy into kinetic energy.

  Claim 100 conveys simply that a person is using a car to drive from one location to another. As for claim 101, it is certainly true that an internal combustion engine converts chemical energy into kinetic energy, but the purpose of driving the car is to move from one place to another, not to convert energy from one form to another. These two claims illustrate the relationship applicants are proposing for claim 38 versus claim 40.

- The structure in claim 44 lacks antecedent basis. If applicants disagree with this assessment, applicants are requested to go back to claim 40, and explain what R^3 and R^4 would have to correspond to in order for the claim dependence to be proper. See also claims 45, 48 and 49.

- Claim 47 recites "the method of claim 39". However, claim 39 is drawn to a compound, not a method. Another error pertains to the following:

  "for use as a protease inhibitor as a composition".

  This appears to be some sort of a hybrid between a compound and a composition. Thus, applicants appear to be commingling issues of compounds, compositions and methods in claim 47. It is suggested that applicants choose just one of these (a compound, a compositions or a method).

- Claim 54 recites the term "caspase-like enzyme", thus rendering the claim indefinite as to the manner in which, or the extent to which, the enzyme must resemble a caspase.

- Claim 54 is drawn to a method of claim 38 for use as an inhibitor to caspase. However, the phrase "for use as an inhibitor to caspase" implies that claim 54 is drawn to a compound, not a method. Further, the claim is indefinite as to the process steps. Exactly how does one use the compound, and separately, how does one use the carrier?

- In claim 54, a number of structures are presented on pages 11 and 12 (of 28 total). In each of these structures, the carbonyl group of the C-terminal aspartyl residue is not sufficiently clear. [The structures must be clear not only to the examiner, but to the persons responsible for printing the final document].

- In claim 54, there are five structures presented on page 11 (of 28 total). In the last of these, furanone ring is linked to the C-terminal aspartyl residue via a peroxide group (i.e., two oxygen atoms bonded to one another). Is this intended?

- In claim 54, there are five structures are presented on page 11 (of 28 total). In the second to last of these, the following group is bonded to the phenyl ring:

$-CH_2-CH_2-NH-O-CO-O-C_6H_5$

It appears that the oxygen atom which is bonded to the imino group is unintended. Is this assessment correct?

- In claim 54, there are four structures presented on page 12 (of 28 total). In each of these, an attempt has been made to depict an indole group at the N-terminus. However, in each of these structures, the C-C double bond (within the five-membered ring) is in the wrong position, i.e., it is in the "1,2" position, rather than the "2, 3" position. In addition, in two of the structures, hydrogen atoms are missing from the amide bond.

- Claim 59 begins with the definite article ("The"). However, it should begin with the indefinite article ("A"), since it is an independent claim.

- Claim 59 recites "The protease inhibitor for use as a pharmaceutical composition". However, this is improper. Applicants can certainly claim compounds *per se*. Applicants can also claim a composition that comprises a compound in combination with a carrier. But a composition is not a use. Applicants have compounded the error in each of claims 60-63; claim 59 is drawn to a protease inhibitor, whereas each of claims 60-63 is drawn to a pharmaceutical composition.

- In claim 64, the phrase "the method of treatment" lacks antecedent basis.

- In claim 65, the phrase "the method of treatment" lacks antecedent basis.

- In claim 66, the phrase "the method of treatment" lacks antecedent basis.

- In claim 67, the phrase "the method of treatment" lacks antecedent basis.

- In claim 68, the phrase "the method of treatment" lacks antecedent basis.

- In claim 69, the phrase "the method of treatment" lacks antecedent basis.

- In claim 70, the phrase "the method of treatment" lacks antecedent basis.

- Each of claims 64-70 is indefinite as to what is meant by an "immune-based disease". In traversing this rejection, applicants are requested to provide two or three examples of diseases which they believe are in no way influenced by, or interface with, the immune system. Such examples will provide the basis for further discussion.

- Each of claims 64-70 recites (last line) "administering ... the compound". However, this renders the claims indefinite as to the objective or target of the administering. For example, if the skilled medical practitioner were to administer the compound to a test tube, would this be effective to improve the memory of a person afflicted with Alzheimer's Disease?

No claim is allowed.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.